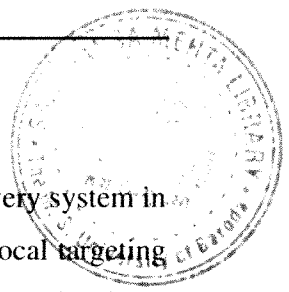
Chapter 1
Introduction



1. INTRODUCTION

Extensive efforts have recently been focused on targeting of a drug delivery system in particular region of the body for extended period of time, not only for local targeting of drugs but also for the better control of systemic drug delivery. Bioadhesion is an integral phenomenon in which two materials, at least one of which is biological, are held together by means of interfacial forces. In the case of polymer attached to the mucin layer of a mucosal tissue, the term mucoadhesion is used. **Mucoadhesion** in drug delivery systems has recently gained interest among pharmaceutical scientists as a means of promoting dosage form residence as well as improving intimacy of contact with various absorption membranes of the biological systems. The mucosal layer lines a number of regions of the body including the nose, gastrointestinal tract, the urogenital tract, the airways, and the eye. This represents potential sites for attachment of any mucoadhesive system and hence, the mucoadhesive drug delivery systems include nasal, oral, buccal, vaginal, rectal and ocular delivery systems (Ahuja et al., 1997).

For systemic therapy, drugs are traditionally administered by oral and parenteral routes. However, in many instances, oral administration is unsuitable when the drug undergoes significant degradation in the gastrointestinal tract or is metabolized to a high degree via the first pass effect in the liver. In addition, the parenteral route can be undesirable or impractical if a drug is intended for the treatment of chronic diseases. Therefore, an alternative route of administration would be preferred (Mao et al., 2003). In recent years, intranasal administration has also been extensively evaluated.

The nasal route appears to be an ideal alternative to the parenterals for administering drugs intended for systemic effect, in view of the rich vascularity of the nasal membranes and the ease of intranasal administration. Besides avoidance of hepatic first pass elimination, the rate and extent of absorption and the plasma concentration versus time profile are relatively comparable to those obtained by IV medication (Ahuja et al., 1997).

Use of mucoadhesive drug delivery system increases the residence time of formulation in the nasal cavity thereby improving absorption of the drugs. Intranasal delivery is needle free and patient-friendly administration route. From a

pharmacokinetic standpoint, absorption is rapid, which should provide a fast onset of action compared to oral and intramuscular administration. Hepatic first pass metabolism is also avoided, allowing increased and reliable bioavailability. Drug degradation that is observed in the gastrointestinal tract is absent. In this regard, good candidates for intranasal delivery are those that undergo extensive first pass metabolism or display erratic absorption.

The **nasal dosage forms** include solutions, sprays, microspheres, gels and liposomes (Mao et al., 1998). Although solutions are easy to use, they achieve a poor bioavailability, due to their short residence time in the nasal mucus. A drug solution is cleared from the nasal cavity into the nasopharynx with an average speed of 6 mm min^{-1}. The average half life of clearance is found to be 15 min. It had been demonstrated that a significant improvement in bioavailability could be achieved when drugs were administered as bioadhesive microspheres without absorption enhancers. Clearance half-lives in the order of 4 h could also be observed.

Using melatonin as model drug, starch microspheres were prepared by Mao et al (Mao et al., 2003) for intranasal administration. It was revealed that > 80% of the starch microspheres could be detected in the nasal tissue 2 h after administration, compared to 30 % for a solution. The absorption rate was rapid, and the absolute bioavailability was high, 84.07%. Microparticulate delivery systems designed for nasal administration of an antiemetic drug, metoclopramide hydrochloride, were prepared by Gavini et al (Gavini et al., 2004). Microspheres composed of sodium alginate, chitosan hydrochloride, or both, were obtained using a spray – drying method. Loratadine-loaded microspheres were prepared by spray-drying of dispersions, emulsions and suspensions differing in polymeric composition and solvents used. Conventional microspheres were obtained by spray - drying of dispersions composed of only chitosan, while composite microspheres were obtained by spray-drying of two-phase systems composed of chitosan and ethyl cellulose (Martinac et al., 2005). The nasal administration of carbamazepine has been studied using microspheres constituted by chitosan hydrochloride or chitosan glutamate. The microspheres were produced using a spray- drying technique. The results obtained indicate that the loading of carbamazepine in chitosan glutamate microspheres increased the amount of the drug absorbed through the nose (Gavini et al., 2006).

In addition to above drugs, other small molecular weight compounds including caffeine (Sachetti et al., 2002), ketorolac (Quadir et al., 2000), metoprolol tartrate, oxaprenolol (Rajinikanth et al., 2003), pentazocine (Preda et al., 2003) and amlodipine besylate (Patil et al., 2006) have been characterized for nasal administration with mucoadhesives.

Hypertension is one of the major risk factors for cardiovascular diseases. It has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years. Data from observational studies indicate that this risk is continuous, without evidence of a threshold, down to blood pressures as low as 115/75 mm Hg. Most cases of hypertension arise through a chronic disease process. More than 90% of cases are idiopathic or primary and are classified as essential hypertension. These have no identifiable cause but have been linked to family history of hypertension, obesity, hemodynamic patterns, vascular hypertrophy, excess dietary sodium, insulin resistance, endothelial cell dysfunction, and hyperactivity of the sympathetic nervous system and renin-angiotensin system. Hypertension develops only in response to an increase in cardiac output and a rise in peripheral resistance. Interplay of various factors, affecting cardiac output and peripheral resistance, may precipitate the disease and differ in both type and degree in different patients (Chiong, 2008).

Hypertension is directly responsible for 57% of all stroke deaths and 24% of all coronary heart disease deaths in India. Indian urban population studies in the mid-1950s used older WHO guidelines for diagnosis (BP≥160 and/or 95 mmHg) and reported hypertension prevalence of 1.2–4.0%. Subsequent studies report steadily increasing prevalence from 5% in 1960s to 12–15% in 1990s. Hypertension prevalence is lower in the rural Indian population, although there has been a steady increase over time here as well. Recent studies using revised criteria (BP≥140 and/or 90 mmHg) have shown a high prevalence of hypertension among urban adults. There is a strong correlation between changing lifestyle factors and increase in hypertension in India. The nature of genetic contribution and gene–environment interaction in accelerating the hypertension epidemic in India needs more studies. Pooling of epidemiological studies shows that hypertension is present in 25% urban and 10% rural subjects in India. At an underestimate, there are 31.5 million hypertensives in

rural and 34 million in urban populations. A total of 70% of these would be Stage I hypertension (systolic BP 140–159 and/or diastolic BP 90–99 mmHg). Recent reports show that borderline hypertension (systolic BP 130–139 and/or diastolic BP 85–89 mmHg) and Stage I hypertension carry a significant cardiovascular risk and there is a need to reduce this blood pressure. Population-based cost-effective hypertension control strategies should be developed (Gupta, 2004).

Carvedilol is a non-selective β-adrenergic antagonist used in the treatment of hypertension and stable angina pectoris (Packer et al., 2002). It is well absorbed orally from the gastrointestinal tract but is subject to considerable first-pass metabolism in the liver; its absolute bioavailability is about 25% (Thummel et al., 2001). Thus, conventional dosage forms of carvedilol (tablets, 6.25 mg/twice a day) suffers from certain disadvantages such as, low oral bioavailability and extensive hepatic first pass metabolism.

Nitrendipine, a lipophilic, dihydropyridine calcium channel blocker used in the treatment of hypertension, has very poor absolute bioavailability (10–20%). Nitrendipine is metabolized in the liver and undergoes extensive first pass metabolism by cytochrome P450 enzyme CYP3A4. A very high degree of variability of pharmacokinetic parameters is observed due to the differences in hepatic metabolism and plasma protein concentration (Soons et al., 1991; Reynolds, 1996).

1.1 Aims and Objectives:

The present investigation was aimed at the development of mucoadhesive delivery systems for nasal administration of the cardiovascular drugs, carvedilol and nitrendipine, with following objectives:

- To formulate microparticulate drug delivery systems with improved mucoadhesion and enhanced contact time which ultimately will increase absorption and hence bioavailability.
- To prevent first pass metabolism of the drugs.

1.2 Proposed Plan of Work:

1. Selection of drugs, excipients and analytical method selection / development.
2. Formulation of mucoadhesive microparticles of chitosan and alginate.
3. Optimization of process and formulation variables.
4. In vitro characterization and evaluation of developed formulations.
5. Histological studies.
6. Stability studies.
7. *In vivo* studies of the optimized formulation to study the pharmacokinetic parameters.
8. Gamma scintigraphy to study the deposition, distribution and subsequent clearance of microspheres.

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